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Mixed cationic liposomes for brain delivery of drugs by the intranasal route: The acetylcholinesterase reactivator 2-PAM as encapsulated drug model

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ABSTRACT

New mixed cationic liposomes based on L-α-phosphatidylcholine and dihexadecylmethylhydroxyethylammonium bromide (DHDHAB) were designed to overcome the BBB crossing by using the intranasal route. Synthesis and self-assembly of DHDHAB were performed. A low critical association concentration (0.01 mM), good solubilization properties toward hydrophobic dye Orange OT and antimicrobial activity against gram-positive bacteria *Staphylococcus aureus* (MIC = 7.8 μg mL^{-1}) and *Bacillus cereus* (MIC = 7.8 μg mL^{-1}), low hemolytic activities against human red blood cells (less than 10%) were achieved. Conditions for preparation of cationic vesicles and mixed liposomes with excellent colloidal stability at room temperature were determined. The intranasal administration of rhodamine B-loaded cationic liposomes was shown to increase bioavailability into the brain in comparison to the intravenous injection. The cholinesterase reactivator, 2-PAM, was used as model drug for the loading in cationic liposomes. 2-PAM-loaded cationic liposomes displayed high encapsulation efficiency (~ 90%) and hydrodynamic diameter close to 100 nm. Intranasally administered 2-PAM-loaded cationic liposomes were effective against paraoxon-induced acetylcholinesterase inhibition in the brain. 2-PAM−loaded liposomes reactivated 12 ± 1% of brain acetylcholinesterase. This promising result opens the possibility to use marketed positively charged oximes in medical countermeasures against organophosphorus poisoning for reactivation of central acetylcholinesterase by implementing a non-invasive approach, *via* the "nose-brain" pathway.

1. Introduction

Intranasal route remains one of the elective non-invasiveness routes for the treatment of brain diseases [1]. It is highly appealing in clinical settings due to rapid central action of drug. This expands drug efficiency in emergency treatment [2]. The nasal mucosa allows direct delivery of drugs to the brain bypassing the blood brain barrier (BBB). It avoids hepatic clearance and drug degradation by liver enzymes, and therefore, increases the effect of neurotherapy [3]. Applicability of intranasal route is limited by lipophilicity and molecular weight of drugs [4]. New formulations to maximize the concentration of drugs and new devices for intranasal administration have been developed [5]. To improve drug transfer to the brain and to prolong the residence time of drug in the nasal cavity, several strategies may be employed, namely the use of (i) permeation enhancers, muco-adhesive and heat sensitive gels, or (ii) nano-sized drug carriers. Colloidal nanosized carriers are especially important for brain delivery and targeting of drugs for treatment of neurodegenerative diseases [6]. Intranasal delivery to the brain by using nanosized particles can be carried out for small molecules, as well as for proteins, hormones, vaccines, DNA, *etc*. [7–10]. The

Abbreviations: AChE, acetylcholinesterase; BBB, blood brain barrier; OP, organophosphorus agent; BChE, butyrylcholinesterase; 2-PAM, pralidoxime chloride; SNC, central nervous system; DHDAB, dihexadecyldimethylammonium bromide; DHDHAB, dihexadecylmethylhydroxyethylammonium bromide; POX, paraoxon; Ph, L-α-phoshatidylcholine

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